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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,069	04/10/2001	Marschall S. Runge	D6179CIP	8710

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,069	RUNGE ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 6-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed April 30, 2004. Currently, claims 6-9 are pending.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

It is noted that no IDS has been filed and applicants did not respond to the notice.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 6, 7, 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of either Corral-Debrinski et al (Mutation Research, Vol. 275, pages 169-180,

1992)(referred to as Corral-Debrinski I) or Corral-Debrinski et al (JAMA, Vol. 266, No. 13, pages 1812-1816, October 1991)(referred to as Corral-Debrinski II).

The instant specification defines "oxidative stress" to refer to pathophysiological effects of reactive oxygen species, such as H2O2, superoxide, peroxynitrate, and other reactive oxygen species (page 25 of the specification).

Yan et al. (herein referred to as Yan) teaches in vivo evidence of the relationship of reactive oxygen species and mitochondrial DNA damage in atherosclerosis. Specifically, Yan teaches assaying both diseased and normal human aortic tissues for DNA damage using a gene-specific quantitative PCR assay. Yan teaches designing primers to amplify a fragment of the human mitochondrial genome and a nuclear fragment within the beta-globin gene. Fresh surgical specimens of normal and atherosclerotic human aorta were immediately frozen in liquid nitrogen. Yan reports that mtDNA damage detected in atherosclerotic tissue was 2 to 5 fold higher than that of human aortic samples without evidence of atherosclerosis. The evidence suggest that the average DNA lesion frequency in the mitochondrial genome was approximately four times higher than that in the nuclear B-globin gene (limitations of Claim 6, 7, 8). Yan teaches that the levels of H2O2 and O2- were assessed using a peroxidase-H2O2 formation assay. The results of Yan suggest that an increase in H2O2 and O2- levels in patients with CAD compared to those without CAD, consistent with a correlation between mtDNA damage and ROS generation. Yan teaches that the data suggest that oxidative mtDNA damage may play a role in atherosclerotic lesion development.

Yan does not specifically teach the measurement of mitochondrial DNA damage by measuring mitochondrial mRNA or protein production, or changes in mitochondrial oxidative phosphorylation or ATP production.

However, Corral-Debrinski I teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease. Corral- Debrinski I teaches the H2O2 can react with superoxide to generate hydroxyl radical (OH-) which are extremely reactive (page 170, col. 2). The close proximity of the mtDNA to these reactive molecules in the inner mitochondrial membrane and the deficiency in mtDNA repair systems result in preferential oxidative damage to the mtDNA (page 170, col. 2). Corral-Debrinski I teaches that mtDNA is maternally inherited and mutations accumulate 10-20 times faster in the mtDNA than in comparable nuclear genes (page 170, col. 1). Moreover, as seen in Figure 1, oxidative phosphorylation dysfunction is related to decreased cellular ATP, mitochondrial damage and oxygen radical formation.

Corral-Debrinski II teaches that oxidative physphorylation (OXPHOS) increases oxygen radical generation, damage to mtDNA and reduces adenosine triphosphate synthesis (abstract). A comparison of the mtDNA deletion and OXPHOS transcript levels in normal and ischemic hearts was analyzed and they were increased, supporting the hypothesis that OXPHOS inhibition is associated with increased mitochondrial damage (page 1813, col. 1). Corral-Debrinski II also states OXPHOS transcripts have been seen increased in cancer cells (limitations of Claim 9).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the teachings of Yan directed to

collecting tissue, measuring the amount of mitochondrial DNA damage, determining the amount of DNA damage in a nuclear gene and comparing the amounts as an indicator of oxidative stress in an individuals to measure the amount of DNA damage using a correlation between mitochondrial mRNA production, measurement of mitochondrial protein production, measurement of changes in mitochondrial oxidative phosphorylation or measurement of changes in mitochondrial ATP production. The prior art, namely Corral-Debrinski I and II and Berlett teach correlations between between mitochondrial mRNA production, measurement of mitochondrial protein production, measurement of changes in mitochondrial oxidative phosphorylation or measurement of changes in mitochondrial ATP production and mtDNA damage. For example, Corral-Debrinski I teaches illustrates in Figure 1, oxidative phosphorylation dysfunction is related to decreased cellular ATP, mitochondrial damage and oxygen radical formation. Corral-Debrinski II teaches that oxidative physphorylation (OXPHOS) increases oxygen radical generation, damage to mtDNA and reduces adenosine triphosphate synthesis (abstract). Therefore, the ordinary skilled artisan would have been motivated to have detected mtDNA damage using any particular known indicator for mtDNA damage taught in the art. Any means of determining mtDNA damage indirectly which is correlative with measurement of mtDNA damage would have been obvious to the ordinary artisan at the time the invention was made.

Response to Arguments

The response traverses the rejection. The response asserts Yan is only an abstract that does not constitute enabling disclosure. This argument has been

thoroughly reviewed, but is not found persuasive because the reference provides sufficient teachings to allow the ordinary artisan to perform the method of Yan. The response further asserts that Yan does not teach measurement of mitochondrial DNA damage is correlated with measuring mitochondrial mRNA or protein production. This argument has been thoroughly reviewed, but is not found persuasive because applicant is arguing the references individually, rather the complete combination of all references.

The response argues that Corral-Debrinski I only provides a method of detection of permanent deletion mutations and does not provide any methodology for assessing the temporal equilibrium between incurred DNA damage and DNA repair that more accurately represents the status of oxidative stress. The response also argues that the methods are more accurate and versatile. This argument has been thoroughly reviewed, but is not found persuasive because the claimed invention does not appear to distinguish from the combination of references. The response further asserts that Corral-Debrinski does not suggest the analysis of DNA from tissues other than cardiac tissue. This argument has been thoroughly reviewed, but is not found persuasive because the claim is broadly drawn to any tissue, including cardiac tissue.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The response argues that Corral-Debrinski II teaches that levels of nDNA and mtDNA oxidative phosphorylation transcripts level were increased in ischemic hearts compared to a normal heart which is not in accordance with the instant invention. This argument has been reviewed but is not convincing because the claim is directed to comparing the amount of DNA damage per length of DNA between said mtDNA and said nuclear gene, wherein a greater amount of mtDNA damage per length of DNA than nuclear DNA damage per length of DNA is indicative of an increased amount of oxidative stress in said individual. This argument has been thoroughly reviewed, but is not found persuasive because coronary artery stenosis due to atherosclerosis deprives the cardiac mitochondria of oxygen and substrates resulting in reduced OXPHOS enzymes and increased oxygen radical generation (page 1813, col. 1). Also, as seen in Figure 2, the mtDNA deletions are significantly increased over ischemic hearts which have oxidative stress. Therefore, Corral-Debrinski II clearly suggests that the DNA damage per length. Further, as seen in Figure 3, the nuclear and mitochondrial genes were compared for control and ischemic individuals. Corral-Debrinski II states that "all of the hearts with ischemia due to atherosclerotic heart disease had much higher levels of the mtDNA deletion, between 8-2200-fold increase. This is consistent with the hypothesis that the OXPHOS inhibition in hearts with chronic ischemia dramatically increases mtDNA damage." Therefore, OXPHOS inhibition (oxidative stress) is increased with increased in mtDNA damage which is not inconsistent with the instant claims.

The rejection of Yan in view of either Corral-Debrinski I or II by detection of mtDNA damage using known methods of mRNA production, mitochondrial protein production, measurement of changes in mitochondiral oxidative phosphorylation would have been art recognized means for detection DNA damage.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

4. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of either Corral-Debrinski et al (Mutation Research, Vol. 275, pages 169-180, 1992)(referred to as Corral-Debrinski I) or Corral-Debrinski et al (JAMA, Vol. 266, No. 13, pages 1812-1816, October 1991)(referred to as Corral-Debrinski II) and further in view of Van Houten (US Pat. 5,989,816, November 23, 1999).

Neither Yan, Corral-Debrinski I or II specifically teach treating DNA with FAPY glycosylase prior to PCR amplification.

Van Houten however teaches method for detection DNA damage by detecting 8-oxo-deoxyguanosine (8-oxo-G-lesion) using FAPY glycosylase. Van Houten specifically teaches that the assay efficiently detects most forms of base damage and DNA single and double strand breaks. The FAPY converts the 8-oxo-dG strand break with a glycosylase/endonuclease from E. coli. The DNA was used to determine the number of lesions/17.7kb.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the mtDNA damage methods of Yan in view of Corral-Debrinski I and II with the teachings of Van Houten. Van Houten specifically teaches that to directly measure some DNA lesions it is necessary to first convert the 8-oxodG to a strand break with a glycosylase/endonuclease. Therefore the ordinary artisan would have recognized that strand damage methods with 8-oxodG requires treatment with FAPY to determine the amount of damage. Thus, the ordinary artisan must treat the DNA with FAPY glycosylase prior to PCR amplification for detection of 8-oxo-G lesions.

Conclusion

5. **Claims 6-9 are rejected.**

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571)272-0507

J. Goldberg

Jeanine Goldberg
Patent Examiner
May 23, 2004

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